Appendix A. Reviewers

Expert Area and Organization	Name	Home Institution
Representatives of Professional Associations		
American Association for the Study of Liver Diseases (AASLD)	Henry C. Bodenheimer, Jr., MD	Mount Sinai School of Medicine
The American College of Physicians-American Society of Internal Medicine (ACP-ASIM)	Harold Fallon, MD	National Academy of Science
The American Academy of Pediatrics (AAP)	Samuel Kocoshis, MD	University of Cincinnati School of Medicine
Infectious Diseases Society of America (IDSA)	David Oldach, MD	University of Maryland School of Medicine
Other Clinical Experts		
Infectious diseases	John G. Bartlett	Johns Hopkins University School of Medicine
Infectious disease nursing	Sherilyn Brinkley-Laughton, MSN	Johns Hopkins University School of Nursing
Hepatology	Robert L Carithers Jr, MD	University of Washington, Seattle, WA
Internal medicine and infectious diseases	Lawrence Deyton, MD MSPH	US Department of Veteran Affairs
Adult hepatology	Lorna Dove, MD	Columbia University, New York
Clinical epidemiology and program policy	Roger Gibson, PhD, DVM, MPH	United States Air Force, Richmond, VA
Clinical epidemiology	Murray Krahn	University Health Network, Toronto, Canada
Hepatology	Mark C Mitchell, MD	Carolinas Medical Center
Pediatric hepatology	Kathleen Schwarz, MD	Johns Hopkins University, Baltimore, MD
Hepatology, hepatitis C, intravenous drug abuse and methadone	Diana Sylvestre, MD	University of California, San Francisco, CA
Methodologic Experts		
Developing best practice models for hepatitis C	Michael Chapko, PhD	Veterans Administration Health Services, Seattle, WA
Outcomes researcher and decision analyst	Mark Fendrick, MD	University of Michigan Schools of Medicine and Public Health, Ann Arbor, MI
Assessment of diagnostic technologies	Ben Littenberg, M.D.	University of Vermont
Pharmaceutical assessment	John Ticehurst	Department of Pathology, Johns Hopkins University

Expert Area and Organization	Name	Home Institution
Payor		
Division of medical items and devices, coverage and analysis group	John Whyte, MD MPH	Center for Medicare and Medicaid Services
Consumer Representatives		
Hep C Connection	Anne Jesse	Founding Director

Appendix B. Priority Journals for Handsearching

Priority Journal Titles	**Frequency**
AIDS	every three weeks
Annals of Internal Medicine	semi-monthly
British Medical Journal	weekly
Clinical Infectious Diseases	semi-monthly
Gastroentrology	monthly
Hepatology	monthly
Journal of Infectious Diseases	semi-monthly
Journal of the American Medical Association	weekly
Lancet	weekly
New England Journal of Medicine	weekly

Appendix C. Literature Search Strategy

PubMed Core Strategies

Key Questions 1a-1e

Name: Hepatitis C (Ques. 1a-1e)
Date and Time search last updated: 26-Sep-2001 12:59:03
Database: PubMed
Search: (hepatitis c, chronic[mh] OR hepatitis c[mh]) AND liver/pa AND (biopsy[mh] OR fibrosis[mh] OR liver function tests[mh]) NOT ("addresses"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "historical article"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "letter"[Publication Type] OR "meeting report"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "periodical index"[Publication Type])
Limits: Publication Date from 1996 to 2001, English, Human

Key Questions 2a-2c

Name: Hepatitis C (Ques. 2a-2c)
Date and Time search last updated: 26-Sep-2001 11:44:42
Database: PubMed
Search: ("treatment outcome"[MESH] OR "disease progression"[MESH] OR "disease free survival"[MESH] OR "Carcinoma, Hepatocellular"[MESH] OR pregnancy[MESH] OR demography[MESH] OR "ethnic groups"[MESH] OR "immunologic factors"[MESH] OR "immunologic diseases"[MESH] OR immunosuppression[MESH] OR "organ transplantation"[MESH] OR "drug therapy/adverse effects"[MESH] OR "antiviral agents/adverse effects"[MESH] OR "antiviral agents/therapeutic use"[MESH] OR "mental disorders"[MESH] OR prisoners[MESH] OR institutionalization[MESH] OR Comorbidity[MESH] OR "liver diseases"[MESH] OR "kidney diseases"[MESH] OR genotype[MESH] OR "Drug Therapy, Combination"[MESH]) AND "hepatitis c, chronic/therapy"[MESH] NOT ("addresses"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development

conference, nih"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "historical article"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "letter"[Publication Type] OR "meeting report"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "periodical index"[Publication Type] OR "published erratum"[Publication Type] OR "retracted publication"[Publication Type])
Limits: Publication Date from 1996 to 2001, English, Human

Key Questions 3a&b

Name: Hepatitis C (Ques. 3a-3b)
Date and Time search last updated: 26-Sep-2001 11:37:20
Database: PubMed
Search: hepatitis c, chronic[mh] AND hepatocellular carcinoma[mh] AND (diagnosis[mh] OR diagnosis[sh] OR "biological markers" OR ultrasound OR "image interpretation, computer-assisted" OR "alpha-fetoproteins" OR "serologic tests") NOT ("addresses"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "historical article"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "letter"[Publication Type] OR "meeting report"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "periodical index"[Publication Type])
Limits: Publication Date from 1996 to 2001, English, Human

Appendix D. Literature Abstract Review Form

Record Number: EPC Hepatitis C - Abstract Review **Reviewer:** _____

First Abstract Review: **Abstract review Form:** **Entered by:**_____

Title:

Do not review, because article (check 1 or more)

1 = not in English
2 = does not include human data
3 = no original data
4 = no information relevant to management of Hepatitis C
5 = reports only basic science
6 = does not apply to one of our key questions
7 = meeting abstract (no full article for review)
8 = other : (specify)_____
9 = unclear : get article to decide

Do not continue if any item above is checked. Otherwise, continue to next column and check *at least one box*.

Article relates to Key Questions (Check all that apply)

☐1a) Does use of **liver biopsy improve outcomes** in management of chronic Hepatitis C? ☐**RCT?**
☐1b) Are results of **initial liver biopsy** related to measures of disease progression and outcomes of treatment? ☐**RCT?**
☐1c) Are results of **followup liver biopsies** related to measures of disease progression and outcomes of treatment? ☐**RCT?**
☐1d) What is the utility of **liver biopsy to identify concomitant** liver disease in patients with Hepatitis C? ☐**RCT?**
☐1e) How well do **non-invasive measures of fibrosis** predict findings of liver biopsy in chronic Hepatitis C? ☐**RCT?**
☐2a) What is **efficacy of current treatment options** for chronic Hepatitis C (pegylated interferon, interferon plus ribavarin, or interferon monotherapy)? ☐**RCT?**
☐2b) See Q2a.
☐2c) What are **outcomes of treatment of chronic Hepatitis C** in subgroups? ☐**RCT?**
☐3a) What is the **efficacy of screening tests for HCC** to improve outcomes in chronic Hepatitis C? ☐**RCT?**
☐3b) What are the sensitivity, specificity and predictive **value of screening tests** in detecting resectable HCC in chronic Hepatitis C? ☐**RCT?**

☐ **Reference only**		☐ **Pediatric patients**
☐ **Systematic review**	☐ **Meta-analysis**	☐ **Case report**

Appendix E. Study Quality Review Form - Johns Hopkins Evidence-based Practice Center Hepatitis C Project

Article ID# _____

First author _____ 1st reviewer (initials) _____ 2nd reviewer (initials) _____

Primary reasons for exclusion: (Check all that apply)

- ☐ Not in English
- ☐ Does not include human data
- ☐ Does not apply to one of our key questions
- ☐ Other: (specify): _____
- ☐ Reports only basic science
- ☐ No information relevant to management of Hepatitis C
- ☐ Meeting abstract (no full article for review)
- ☐ All data reported in a subsequent publication

Additional exclusions per Key Question refinements: (Check all that apply)

- ☐ Addresses only KQ1d (Utility of liver biopsy for identifying concomitant liver disease)
- ☐ Addresses KQ2a or c, except not a randomized controlled trial
- ☐ Addresses only KQ2a, but only interferon alone without analysis of subgroups of interest (e.g., patients with renal disease or inability to take ribavirin)
- ☐ Addresses only KQ2b (Extent of inclusion of patient subgroups in randomized controlled trials)
- ☐ Addresses KQ2d, but has < 5 years (60 months) of followup

Study quality exclusions: (Check all that apply)

For all Questions

☐ **Outcomes were not measured using an appropriate objective standards.**

Objective Standards:

For Q1b, c: Virologic and/or histologic measures

For Q1e: Liver biopsy with at least 1 cm length or 3 portal triads

For Q2a, c, d: Virologic and/or histologic measures

For Q3a: Histologic/pathologic evidence (in at least 50% of patients with abnormal screening tests, and at least 6 months of followup) and/or mortality

For Q3b: Histologic/pathologic evidence

☐ **Total study population < 30** (specify N:_____)

For key questions 1b, 1c, 2a, 2c, and 3a

☐ **The planned length of followup was less than 6 months**

If ANY of the above items is CHECKED ➜STOP: Do Not Continue; return article and form to Mollie

Does article address a Key Question? (Check all that apply)

Biopsy

☐ KQ1a: Deleted

☐ KQ1b: How well do results of **initial liver biopsy** predict measures of disease progression and treatment outcome?

☐ KQ1c: How are results of **followup liver biopsies** related to measures of disease progression and treatment outcome?

☐ KQ1d: Deleted

☐ KQ1e: How well do **non-invasive measures** of fibrosis predict the findings of liver biopsy?

Treatment options

☐ KQ2a: To what extent have **randomized controlled trials** shown the **efficacy and safety of current treatment options** for chronic Hepatitis C (pegylated interferon, interferon plus ribavarin, or interferon)?

☐ KQ2b: Deleted

☐ KQ2c: According to randomized controlled trials, what is the **efficacy and safety of current treatment options** for chronic Hepatitis C in subgroups (e.g., by age, viral genotype, prior treatment status, or presence of cirrhosis, decompensated liver disease, Hepatitis B, or HIV)?

☐ KQ2d: What are the **long term outcomes** (≥5 years) of current treatment options for chronic Hepatitis C

Screening tests

☐ KQ3a: What is the **efficacy of screening tests for hepatocellular carcinoma** to improve outcomes in chronic Hepatitis C?

☐ KQ3b: What are **sensitivity, specificity and predictive value of screening tests** for detecting curable hepatocellular carcinoma in Hepatitis C patients?

REPRESENTATIVENESS OF STUDY POPULATION

6. Did the study describe the setting and population from which the study sample was drawn, and the dates of the study?

a. Adequate	(Setting AND population described AND start and end date specified)	2
b. Fair	(One or more of these NOT reported OR poor description)	1
c. Inadequate	(Not specified)	0
d. Not applicable		N/A

7. Were detailed inclusion/exclusion criteria provided?

a. Adequate	(Detailed description of specific inclusion and exclusion criteria OR statement that all eligible patients enrolled)	2
b. Fair	(Some description, but would be difficult to replicate based on information provided)	1

c. Inadequate	(Minimal description or none at all)	0
d. Not applicable		N/A

8. Was information provided on excluded or not participating patients?

a. Adequate	(All reasons for exclusion AND # excluded OR no exclusions)	2
b. Fair	(Only one of above criteria specified or information not sufficient to allow replication)	1
c. Inadequate	(None of the above criteria specified)	0
d. Not applicable		N/A

Item 9 for key question 1 only

9. Did the study include an appropriate spectrum of patients with chronic hepatitis C? (e.g., not only elderly patients with, for example, decompensated liver disease)?

a. Adequate	(Wide range of age AND wide range in severity of disease)	2
b. Fair	(Wide range of age OR wide range in severity of disease)	1
c. Inadequate	(Neither)	0

10. Does the study describe key patient characteristics at enrollment?

***Demographics*:** age; gender

Hepatitis C Features: genotype; degree of fibrosis or cirrhosis; minimal or decompensated liver disease

a. Adequate	(Demographic and Hepatitis C features well described)	2
b. Fair	(Only demographics well described)	1
c. Inadequate	(No key patient characteristics well described)	0
d. Not applicable		N/A

BIAS AND CONFOUNDING

POINTS

Item 11 for key questions 2a, 2c, 2d, and 3a

11. Was assignment of patients to study groups randomized?

a. Yes	(Investigators could not predict assignment)	2
b. Partial	(Date of birth, admission date, hospital record number, or other non-random scheme for assignment OR did not state method of randomization)	1
c. Not randomized		0
d. Unclear		0
e. Not applicable		N/A

Item 12 for key questions 2a, 2c, 2d, and 3a

12. Did the patient groups have any important differences on key patient characteristics?

***Demographics*:** age; gender

Hepatitis C Features: e.g., genotype, degree of fibrosis or cirrhosis, minimal or decompensated liver disease

a.	Groups equivalent in all factors examined	2
b.	Groups have minor difference in 1 or 2 factors	1.5
c.	Groups have an important difference in one or more factors OR minor differences in more than 2 factors	1
d.	Analysis not done	0
e.	Not applicable	N/A

Item 13 for key questions 2a, 2b, 2d, and 3a

13. Was there blinding of clinicians, patients, and outcome assessors?

a. Excellent	(All three blinded, including all treatment arms)	2
b. Good	(Only 2 of the 3 blinded, or some but not all of the arms blinded in all 3 ways)	1.5
c. Fair	(Only 1 of the 3 blinded)	1
d. Poor	(No blinding or not stated)	0
e. Not applicable		N/A

Item 14 for key questions 1b, 1c, 1e, 3b

14. Was there an independent blind comparison with a reference standard (i.e., virologic/histologic evidence for 1b or c, histologic evidence for 1e, and histologic/pathologic evidence for 3b) at initial assessment and a blinded assessment or follow up?

a. Adequate	(Independent AND blind)	2
b. Fair	(Independent OR blind)	1
c. Inadequate	(Neither)	0
d. Not applicable		N/A

DESCRIPTION OF THERAPY/MANAGEMENT

Item 15 for key question 1 only

15. Did the study describe the technique and size of the liver biopsy?

Technique: Percutaneous transhepatic or transjugular
Sample size: Length and/or number of portal triads

a. Adequate	(BOTH characteristics described)	2
b. Fair	(ONE characteristic described)	1
c. Inadequate	(NEITHER described)	0
d. Not applicable		N/A

Item 16 for key question 2 only

16. Did the study describe details of the treatment regimen?

a. Adequate	(Name of drugs, dose, AND duration described)	2
b. Inadequate	(One of more of above NOT described)	0
c. Not applicable		N/A

Item 17 for key question 3 only

17. Did the study describe details of the screening test(s)?

a. Adequate	(Exact type of test AND frequency of test described)	2
b. Fair	(Exact type of test OR frequency of test described)	1
c. Inadequate	(Neither described)	0
d. Not applicable		N/A

Item 18 for key questions 2a, 2c, 2d, and 3a

18. Was there a description of other treatments and tests given to each study group?

Other treatments: Anti-retroviral drugs, antidepressants, erythropoietin, granulocyte colony stimulating factor, etc.
Other tests: Serologic, virologic, radiologic, etc.

a. Adequate	(Other treatments and tests fully described)	2
b. Fair	(Some description, but information not sufficient to allow replication)	1
c. Inadequate	(Not described or not mentioned)	0
d. Not applicable		N/A

OUTCOMES AND FOLLOWUP

19. Did the study describe complications, side effects, and adverse reactions experienced by patients?

Biopsy: Pain, bleeding, infection, death
***Treatment*:** Depression, thyroid dysfunction, cytopenia, portal hypertension
***Screening*:** Contrast reactions, procedure complications

a. Adequate	(Complications, side effects, AND adverse reactions described fully)	2
b. Fair	(Complications, side effects, OR adverse reactions mentioned, but NOT described fully)	1
c. Inadequate	(Complications, side effects, AND adverse reactions NOT mentioned)	0
d. Not applicable		N/A

20. Was there a description of the criteria for determining outcomes?

a. Adequate	(Clear definitions of each outcome AND exact techniques to assess the outcome)	2
b. Fair	(Some description, but information not sufficient to allow replication)	1
c. Inadequate	(No information provided)	0
d. Not applicable		N/A

21. No item 21

22. Did the study report the numbers of and reasons for withdrawals from the study protocol or patients otherwise lost to follow-up?

a. Numbers and reasons reported (or no withdrawals)	2
b. Only numbers OR reasons reported	1
c. Neither given	0
d. Not applicable	N/A

23. What was the greatest percentage of patients in a treatment/screening study group that withdrew from the study protocol or were lost to follow-up?

a. None	2
b. < 10%	1.5
c. 10 - 20%	1
d. >20%	0
e. Not stated	0
f. Not applicable	N/A

Item 24 for key questions 1b, 1c, 2a, 2c, 2d, and 3a

24. What was the planned length of followup?

a. > 5 years	2
b. 1-5 years	1.5
c. 6 - 11 months	1
d. 0 - 5 months	0
e. Not applicable ***(key question 1e and 3b)***	N/A

STATISTICAL QUALITY AND INTERPRETATION

25. For primary endpoints, did the study report the magnitude of difference between groups (or magnitude of association between key variables) AND an index of variability (e.g., test statistic, *p* value, standard error, confidence interval)?

a. Adequate	(Both reported, with standard error or confidence intervals as index of variability)	2
b. Fair	(Both reported, with only test statistic or *p* value as index of variability)	1
c. Inadequate	(No information given)	0
d. Not applicable		N/A

26. Was the statistical test for all analyses clearly identified?

a. Adequate	(Identified for all analyses)	2
b. Fair	(Identified for some of the analyses)	1
c. Inadequate	(Not identified)	0
d. Not applicable		N/A

Item 27 for key questions 2a, 2c, 2d, and 3a

27. If groups were not comparable at study onset, was there adjustment for potential confounders with multivariate or stratified analyses AND were confounders coded in a way to make such control adequate?

a. Adequate	(Adjustment AND confounders appropriately coded)	2
b. Fair	(Adjustment BUT confounders not coded appropriately OR coding unclear)	1
c. Inadequate	(No adjustment OR not mentioned)	0
d. Not applicable		N/A

28. Were withdrawals, crossovers, and loss to follow-up handled appropriately in analysis?

a. No loss to followup, withdrawals, or crossovers	2
b. Sensitivity analysis	2
c. By intention to treat/screen	2
d. By 'intervention received' analysis only	1
e. By none of the above	0
f. Unknown	0
g. Not applicable	N/A

CONFLICT OF INTEREST

29. Did the study report identify the source of funding and the type and degree of involvement of the funding agency?

a. Adequate	(Source AND type or degree of involvement OR no funding)	2
b. Fair	(Source only)	1
c. Inadequate	(Neither)	0
d. Not applicable		N/A

THANK YOU for your time and attention to completing this work.
Please return completed form to Mollie.